

REMARKS

Compliance of the IDS of November 26, 2001

The Examiner indicates that the IDS filed on November 26, 2001 was not in proper form because no form PTO-1449 was included. However, as indicated on the attached copy of the stamped postcard, a form PTO-1449 was included with the IDS when filed. An additional copy is attached hereto for the Examiner's convenience and consideration of the listed references. Applicants request that an initialed copy of the form PTO-1449 be returned to them upon consideration of the references.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. §112, second paragraph as being unclear. More specifically, claim 1 has been rejected for the reasons indicated in Items 7-10 of the Office Action and claim 8 has been rejected for the reason indicated in Item 11 of the Office Action. Claims 1 and 8 have been amended as indicated above, to address these issues and clarify the claims. Withdrawal of the rejections is therefore respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1, 2, 5-7, 9 12, 13, and 14 have been rejected under 35 U.S.C. §103 as being obvious over Dattagupta et al. (U.S. Pat. No. 6,380,377) combined with Dahlberg et al. (U.S. Pat. No. 5,837,450).

Dattagupta is asserted to teach a hairpin nucleic acid probe having a stem region and a loop region, wherein the stem region has a restriction enzyme cleavage site and the loop region can form a duplex with target nucleic acid under suitable conditions. Dattagupta is asserted to differ from the invention in showing the removal of the cleavage site by the hybridization of the loop region to a fully complementary target. However, the Examiner asserts that this feature is "considered to be a capability" of the hairpin probe of Dattagupta. Dattagupta is further asserted to differ from the invention with the inclusion of a label on one end of the probe.

Dahlberg et al. is asserted to teach a hairpin probe having a label on one end and the release of that label by cleavage of the probe. The Examiner asserts that based on the disclosure in Dahlberg et al. it would be obvious to add a label to the probe of Dattagupta. The Examiner further asserts that a hairpin probe having 16-25 bases in the loop sequence is an obvious modification of the disclosures of Dattagupta and Dahlberg et al.

Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The present invention, as encompassed by claim 1 is drawn to a nucleic acid probe for detecting hybridization of unlabeled nucleic acid comprising:

an oligonucleotide having two terminal ends with

(a) a surface-coupling group, attached to one terminal end of the oligonucleotide,

(b) a "loop sequence" that is complementary to a target nucleic acid sequence;

(c) a "stem structure," containing a restriction enzyme cleavage site that is not present when the loop sequence (b) is hybridized to the target nucleic acid sequence; and

(d) a label attached to the other terminal end of the oligonucleotide, wherein cleavage by a restriction enzyme specific for the restriction site of the stem sequences detaches the label from the surface;

and wherein hybridization of a fully complementary target nucleic acid to the loop sequence breaks the intramolecular hybridization bonds of the stem structure and removes the restriction site.

Dattagupta discloses an oligonucleotide probe containing a hairpin loop. However, Dattagupta differs from the present in that the method of the reference requires that the portion of the probe sequence that takes part in intermolecular hybridization to the target DNA must be part of the sequence that is involved with the intramolecular hybridization, i.e. the target binding portion must be at least partly located within the stem portion of the hairpin. See for example the column 1, lines 18-23, which state,

The probes each comprise a nucleotide sequence which, under suitable conditions, is capable of forming a hairpin structure having a nucleotide sequence complementary to a target nucleotide sequence to be detected located within the double stranded segment. (emphasis added)

See also claim 1 of Dattagupta. It is evident from the disclosure in Dattagupta that it is essential for the method disclosed in the reference that a portion of the nucleotide sequence complementary to the target nucleotide sequence be located within the double stranded hairpin region of the probe. This feature is completely opposite to the mechanism of present invention and would result in the present invention being inoperable. The present invention requires that the nucleotide sequence complementary to the target nucleotide sequence be located solely within the loop region. It is essential for the present invention that the nucleotide sequence complementary to the target nucleotide sequence be located solely within the target region to prevent the label from being cleaved if the target sequence is present. Thus, the Dattagupta differs from the present invention in more than simply not including a label on the probe. Dattagupta is fundamentally different from the present invention and fails to disclose the essential feature of the invention of having the nucleotide sequence complementary to the target nucleotide sequence located solely within the loop region such that upon binding to a target nucleic acid, the restriction

enzyme cleavage site is lost and the label remains bound to the probe.

Dahlberg et al. fails to compensate for the deficiencies of Dattagupta. In the method of Dahlberg et al., the restriction site is formed by annealing complementary molecules to the target nucleic acid. See column 7, lines 17-63. With the present invention, the complete opposite occurs in that the restriction site is destroyed by annealing the target nucleic acid to the probe. In addition, Dahlberg et al. works by the detection of label following digestion, whereas with the present invention, the label is detected in the undigested probe. Finally, Dahlberg et al. differs from the present invention in the use of a special nuclease that specifically cleaves double-stranded nucleic acid into single-stranded products. The restriction enzyme of the present invention cuts the double strand across both strands, leaving double-stranded products and the present invention relies on the weakness of the cleaved stem structure to remove the portion of the probe containing the label. Thus, Dahlberg et al. is also fundamentally different from the present invention and similarly fails to teach the feature of having the complementary nucleic acid sequence to the target nucleic acid located within the loop region such that if the target nucleic acid is present, the digestion site is lost and the label remains bound to the probe. As such, the present invention is not achieved by combining Dattagupta with

Dahlberg et al. and withdrawal of the rejection is respectfully requested.

Claim 4 has been rejected under 35 U.S.C. §103 as being obvious over Dattagupta combined with Dahlberg et al. and Kacian et al. Kacian et al. is relied on for teaching the use of an acridium label with a DNA probe.

Claim 10 has been rejected under 35 U.S.C. §103 as being obvious over Dattagupta combined with Dahlberg et al. and Johnson et al. Johnson et al. is asserted to teach nucleic acids having a polythymine spacer.

Claim 11 has been rejected under 35 U.S.C. §103 as being obvious over Dattagupta combined with Dahlberg et al. and Beattie. Beattie is asserted to teach the covalent attachment of an oligonucleotide having an aminopropanol at its 3' end to a solid support.

Kacian et al., Johnson et al. and Beattie similarly fail to disclose the features of the present invention, which are absent in Dattagupta and Dahlberg et al. As such, the invention of claims 4, 10 and 11 is not achieved by or obvious over the references. Withdrawal of the rejections is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an

interview in an effort to expedite prosecution in connection with the present application.

A marked-up version of the amended claims showing all changes is attached hereto.

Applicants request a one (1) month extension of time for responding to the Restriction Requirement. The required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Enclosures: Marked-up claim copy
Copy of 11/20/2001 Form PTO-1449
Copy of USPTO-stamped postcard showing 11/20/2001
Form PTO-1449 was received

(Rev. 01/02/02)

MARKED-UP VERSION SHOWING CHANGES

IN THE CLAIMS

Claims 1 and 8 have been amended as follows.

1. (Amended) A nucleic acid probe for detecting hybridization of unlabeled nucleic acid comprising :

an oligonucleotide having two terminal ends with

(a) a surface-coupling group, attached to one terminal end of the oligonucleotide,

(b) a first sequence called the "loop sequence" that is complementary to a target nucleic acid sequence;

(c) a second sequence and a third sequence, which are located on opposite ends of the loop sequence which ~~can~~ hybridize to each other in the absence of the target nucleic acid sequence to form ~~is~~ called a "stem structure," wherein said stem structure contains a restriction enzyme cleavage site that is not present when ~~in~~ the loop sequence (b) ~~when~~ is hybridized to the target nucleic acid sequence; and

(d) a label attached to the other terminal end of the oligonucleotide wherein ~~located on the opposite side of the restriction site from the surface coupling group such that~~ cleavage by a restriction enzyme specific for the restriction site of the stem sequences detaches the label from the surface;

~~wherein said loop sequence makes up all, or part, of the nucleotides between the complementary sequences,~~ and wherein hybridization of ~~the~~ a fully complementary target nucleic acid to the loop sequence breaks the intramolecular hybridization bonds of the stem structure and removes the restriction site.

8. (Amended) The nucleic acid probe of claim 1, wherein the label is biotin and is attached to the oligonucleotide through a biotin-steptavidin coupling.